

- 2 -

Commissioner of Patents and Trademarks

1. (Currently Amended) A method for the diagnosis of a metabolic bone diseases disease in a patient, said method comprising ~~which comprises~~ the step of determining the level of PTHrP a substrate of PEX in a biological sample of a said patient wherein an alteration of PTHrP in the levels level of said substrate from that of a normal individual is indicative of a metabolic bone diseases disease and/or a metabolic bone disease predisposition.
2. (Currently Amended) The method of claim 1, wherein said metabolic bone diseases disease is osteomalacia, osteoporosis, osteopetrosis, ~~or~~ Paget's disease or X-linked hypophosphatemic rickets.
3. (Currently Amended) A method for the treatment of metabolic bone diseases dis-
ease, ~~which comprises~~ said method comprising administering to a patient a compound for the modulation of PEX enzymatic activity wherein said compound modulates PTH and/or PTHrP levels that regulate osteoblast activity.
4. (Currently Amended) The method of claim 3, wherein said metabolic bone diseases disease is osteomalacia, osteoporosis, osteopetrosis, ~~or~~ Paget's disease or X-linked hypophosphatemic rickets.
5. (Currently Amended) Use of a compound for the modulation of PEX enzymatic activity for the manufacture of a medicament for treating a metabolic bone diseases disease, wherein said compound modulates PTH and/or PTHrP levels that regulate osteoblast activity.
6. (Currently Amended) The use of claim 5, wherein said metabolic bone diseases disease is osteomalacia, osteoporosis, osteopetrosis, ~~or~~ Paget's disease or X-linked hypophosphatemic rickets.
7. (Currently Amended) A method for ~~the treatment~~ treating of metabolic bone diseases disease, ~~which comprises~~ said method comprising modulating PTH and/or PTHrP levels that regulate osteoblast activity in a patient to modulate bone breakdown and/or bone formation.
8. (Currently Amended) The method of claim 8, wherein said metabolic bone diseases disease is osteomalacia, osteoporosis, osteopetrosis, ~~or~~ Paget's disease or X-linked hypophosphatemic rickets.

- 3 -

Commissioner of Patents and Trademarks

9. (Currently Amended) Use of a compound for the modulation of PTH and/or PTHrP levels that regulate osteoblast activity for the treatment of a metabolic bone diseases disease.
10. (Currently Amended) The use of claim 9, wherein said metabolic bone diseases disease is osteomalacia, osteoporosis, osteopetrosis, or Paget's disease or X-linked hypophosphatemic rickets.
11. (Original) A non-human transgenic mammal to study the role of PEX in bone development and homeostasis, whose germ cells and somatic cells contain a PEX gene construct for expression of PEX in osteoblast consisting essentially of a recombinant PEX gene sequence under the control of a proximal promoter of a pro- α 1(I) collagen gene, the PEX gene construct being introduced into the mammal, or an ancestor of the mammal, at an embryonic stage.
12. (Original) The non-human mammal of claim 11, which is a mouse and the proximal promoter is murine pro- α 1(I) collagen gene.
13. (Original) The non-human mammal of claim 12, wherein said murine pro- α 1(I) collagen gene is a 2.3 kb fragment thereof.
14. (New) The method of claim 1 wherein said substrate is parathyroid hormone (PTH) or parathyroid hormone-related peptide (PTHrP).
15. (New) A method of identifying a compound that modulates PEX enzymatic activity, the method comprising: (i) contacting PEX with a substrate for PEX and a test compound; and (ii) determining whether degradation of the substrate is modulated in the presence of the test compound; wherein when degradation of the substrate is modulated said compound is identified as having a therapeutic potential for PEX modulation.
16. (New) The method of claim 15 wherein said substrate is parathyroid hormone (PTH) or parathyroid hormone-related peptide (PTHrP).
17. (New) The method of claim 16 wherein said modulation is a decrease in PEX enzymatic activity.
18. (New) The method of claim 15 wherein said substrate is PTH and said modulation is an increase in PEX enzymatic activity.

- 4 -

Commissioner of Patents and Trademarks

B1
cont

19. (New) The method of claim 15 further comprising: (iii) selecting said compound as a candidate compound for treating metabolic bone disease in a mammal.
-